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TITLE: Immunomodulation to Optimize Vascularized Composite Allograft Integration in Limb Loss Therapy

PRINCIPAL INVESTIGATOR: Linda C. Cendales, MD

CONTRACTING ORGANIZATION: Emory University
Atlanta, GA 30322

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14. ABSTRACT Recent improvements in body armor have reduced the rate of combat death but increased the rate of extremity injury, burn and limb loss in surviving casualties. As such, methods to replace injured limbs are increasingly required to support combat service personnel. Vascularized composite alltransplantation (VCA) has recently emerged as a promising strategy for the repair or replacement of amputated limbs, and novel methods for immune management to prevent the rejection of transplanted tissues are now available that may greatly reduce the risks associated with limb transplantation.					
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I. Introduction

Recent improvements in body armor have reduced the rate of combat death but increased the rate of extremity injury, burn and limb loss in surviving casualties. As such, methods to replace injured limbs are increasingly required to support combat service personnel. Vascularized composite allotransplantation (VCA) has recently emerged as a promising strategy for the repair or replacement of amputated limbs, and novel methods for immune management to prevent the rejection of transplanted tissues are now available that may greatly reduce the risks associated with limb transplantation.

The proposal will utilize a comprehensive approach to efficiently apply the newest clinically proven methods of modulation of the immune system to lower the risk and improve the benefits of patients after limb reconstruction through transplantation. The study provides a new platform to optimize integration of a limb after limb loss with a therapy based on a once a month medication. The entire study addresses the increase clinical need of limb loss seen in the current combat conflicts. The intervention provides the reconstruction of skin, muscle, tendon, bone, nerve, and vessels as a functional unit (limb) in individuals who suffered limb loss. The treatment includes the newest medication recently

approved by the US Food and Drug Administration. Studies will define the efficacy of the newest medication on protective immunity and the mechanisms of graft rejection. Additionally, the studies will be conducted concurrently to determine in objective terms the integration of the recipients use of their transplanted limb compared to their pre-transplant state. Moreover, evaluation of the recipient's quality of life will be performed.

II. Body

Task 1. : To use an efficacious immunomodulation regimen based on belatacept to optimize the integration of limb transplantation after limb loss.

Regulatory Review and Approval Process

During this reporting period the PI relocated from Emory University to Duke University with a start date of April 1, 2014. Emory relinquished the award and Duke submitted the final documents on August 11, 2014. At this time, we are awaiting the completion of the transfer from the funding agency.

Clinical Trial

Our studies are under an Institutional Review Board (IRB) approved protocol entitled "Immunomodulation to Optimize Vascularized Composite Allograft Integration in Limb Loss Therapy".

The funding agency approved the submission of the protocol to the Duke Institutional Review Board on September 16, 2014. We received regulatory approval of the protocol from the Duke IRB on November 14, 2014. At this time we are awaiting institutional approval before the documents are submitted for review to the Human Research Protection Office (HRPO).

During this reporting period we submitted the protocol to the Emory IRB and HRPO. The IRB granted full approval of the protocol on October 23, 2013. The proposal was subsequently submitted to HRPO. The protocol was reviewed by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), and found to comply with applicable DOD, US Army, and USAMRMC human subjects protection requirements on November 5, 2013.

During the next reporting period the transfer will be completed and we plan to finalize the study protocol institutional and regulatory approvals. We plan to initiate the screening of potential candidates for limb transplantation. A potential problem area in the next phase of the study will be recruitment. For that purpose, we submitted recruitment letters and documents, which were approved by the IRB. We intent to distribute the approved documents to DoD and Civilian centers nation-wide. We also plan to complete the registration of the study at Grants.gov for website access.

Site Visit

On November 3, 2014 we received a site visit from the funding agency. The agenda included various presentations of the resources at Duke supporting the Vascularized Composite Allotransplantation Program and a tour of the facilities.

III. Research Accomplishments

- a. IRB approval of the study protocol.
- b. The annual report of the IND 113,206, Nulojix (Belatacept) was submitted to the FDA. Sponsor: Linda C. Cendales, MD

IV. Reportable outcomes

N/A to this study period

V. Conclusion

This entire study addresses the increase clinical need of limb loss seen in the current combat conflicts. The intervention provides the reconstruction of skin, muscle, tendon, bone, nerve, and vessels as a functional unit (limb) in individuals who suffered limb loss.